UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,570	08/16/2006	Michael Betz	BP/G-32576A/BCK	5942

72554 7590 01/07/2008

SANDOZ INC
506 CARNEFIE CENTER
PRINCETON, NJ 08540

EXAMINER	
HA, JULIE	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
01/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,570	BETZ ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,14,15 and 18-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,14,15 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-Final rejection filed on September 12, 2007 is acknowledged.

Claims 1-10, 12, 14, 15 and 18-23 have been examined in the previous office action and in this office action.

Julie Ha is the Examiner of record.

Withdrawn Objections and Rejection

1. Objection to the specification and claim 22 are hereby withdrawn due to Applicant's amendment to claim 22.

2. Rejection under 35 U.S.C. 112, 1st paragraph of claim 22 is hereby withdrawn due to Applicant's amendment to the claim.

Maintained Rejection

35 U.S.C. 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-10, 12, 14-15 and 18-23 rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor et al (US Patent # 5763394), issued June 9, 1998 (filed July 29, 1993 as PCT/US93/07149) as applied to claims 1-10, 12, 14-15 and 18-23 above.

6. O'Connor et al describe in their claim 9 a human growth hormone formulation comprising human growth hormone (referred to hereafter as hGH) in the concentration range of 1-20 mg/ml, contained in a buffer system providing a pH of 5.5-7, a non-ionic surfactant, and a neutral salt. At column 3, lines 27-32, the mixture has no requirement for glycine, however, glycine is "an optional component of the aqueous formulation." They omit it from their claimed formulation because it provides "less advantage in the aqueous formulations hereof" and allude to the fact that glycine is more advantageous in preparations that have at some point been lyophilized. The range of hGH claimed by O'Connor et al overlaps the range claimed in the instant claim 1 and completely encompasses the preferred range and single value in the instant claims 2 and 3. O'Connor et al discuss the role of glycine in the Background of their invention in column 1 of the '394 patent, citing commercial preparations that contain glycine (column 1, lines 30 and 42) and column 2, line 7). The latter reference is in the context of O'Connor et al's formulation having the unexpected advantage of being more stable with glycine absent, contrary to the common practice in the art. O'Connor et al do recite the value of

5 mg/ml in the abovementioned line 32, column 1 as being part of the commercially marketed Humatrope® formulation, this value being at the low end of the range claimed in the instant claim 5. O'Connor et al describe their preferred embodiments as having quantities of components somewhat flexible within the component categories, allowing for instance, for additional buffering agent (see column 4, lines 19-39).

7. The instant claim 6 claims that the instant composition should be "substantially isotonic" and O'Connor et al state that "preferably, the formulation is isotonic and sterile" (see column 4, lines 27-28). O'Connor et al state that the buffers for their composition include phosphate, citrate, and acetate, comprising three of buffer choices from the instant claim 7, and the phosphate buffer of the instant claim 8; O'Connor et al further claim phosphate buffer in their claim 16. O'Connor et al state that suitable buffers are formulated in the range of "about 2 mM to about 50 mM" and when formulated with their other components the final mixture has a pH value of "about pH 6" (see claims 7 And 15) which, in conjunction with their claimed pH range of 5.5-7 in their claim 1, is similar to and encompasses the pH range in the instant claim 1 and the value of pH 6.2 in the instant claim 21.

8. The instant claim 1 and 12-15 claim a non-ionic surfactant, poloxamer and polysorbate being specified in claims 12-15. O'Connor et al claim Poloxamer 188 in their claim 2, 3, 10 and 11 and polysorbates in their claims 4, 5, 12 and 13. O'Connor et al state a broad range of surfactant concentrations, from 0.1% to 5% w/v, with 0.1% to 1% w/v preferred (column 3, lines 33-45), overlapping the instant claims. The instant claim 18 claims preservatives, and claims 19 and 20 specify benzyl alcohol. O'Connor et al

state that their list of acceptable preservatives includes several of those from the instant claim 18, most particularly phenol and benzyl alcohol (column 3, lines 52-56), the latter cited in a range of 0.7-1% w/v, overlapping the range of the instant claim 20. Furthermore, O'Connor et al teach a kit: six vials of lyophilized growth hormone, water for injection, and six vials of the hGH aqueous formulation transferred to 3 cc vials (see Example II). Furthermore, O'Connor et al teach that addition of preservative is included in the formulation to retard microbial growth and thereby allow "multiple use" packaging of the hGH (see column 3, lines 50-52).

9. In summary: there is a prima facie case of obviousness in regards the instant claims when compared to the prior art cited above. The prior art discloses all of the aspects and limitations of the instant invention, either specifically, such as the use of the surfactant Poloxamer 188, or with ranges of values that encompass or overlap those claimed by Applicant, such as the quantities of the active ingredient hGH, or as alternative choices of materials to be used to achieve the same result, such as the choice of buffer system or preservative. The claimed ranges and values for the amount of glycine that are greater than those typically found in the art are obvious in that it has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Response to Applicant's Arguments

10. Applicant argues that "all of the formulations disclosed in O'Connor et al contain either mannitol or a neutral salt, with preferred embodiment of the disclosed formulations consists of or consisting essentially of hGH, nonionic surfactant, buffer and either a neutral salt or mannitol." Applicant argues that "the invention of the present claims does not include either a neutral salt or mannitol...furthermore, the formulations taught by O'Connor et al Are stated to provide unexpected benefits in the absence of glycine." Further, Applicant argues that the Office makes no attempt to establish that O'Connor et al teaches a liquid formulation which has a tonicity of from about 100 to about 500 mosm/kg...O'Connor et al teaching of a liquid formulation that is 'preferably isotonic' is not sufficient to render obvious a formulation with a permissible range of tonicity as recited in the present claims." Finally, Applicant argues that there is no prima facie obvious to "select optimal parameters" in a formulation "to achieve a beneficial result" since O'Connor teaches away from the present invention.

11. Applicant's arguments have been fully considered but have not been found persuasive because O'Connor et al teaches the components of hGH formulation that is prima facie obvious to one of ordinary skilled in the art. O'Connor et al teach hGH liquid formulation comprising all of the components of the present invention. O'Connor et al teaches that the formulation has hGH and that glycine is an optional component of the aqueous formulation "although with less advantage in the aqueous formulations compared with those formulations that are lyophilized for later reconstitution...amounts of glycine will range from 0 mg/ml to about 7 mg/ml". This implies that glycine can be

added to the liquid formulation. Furthermore, a person of ordinary skill in the art would have tried to optimize the formulation stabilization conditions, since O'Connor indicate that US Patent # 4297344 discloses stabilization of coagulation factors II and VIII, antithrombin III, and plasminogen against heat by adding selected amino acids such as glycine, alanine (see column 1, lines 40-43) and Australian Patent Application NO. AU-A-30771/89 teaches stabilization of growth hormone using glycine and mannitol (see column 2, lines 3-5).

12. It has been held that under KSR that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in KSR, When there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727,_,82 USPQ2d 1385, 1397 (2007).

13. The "problem" facing those in the art was hGH undergoes several degradative pathways, especially deamidation, aggregation, clipping of the peptide backbone and oxidation of methionine residues, and there were a limited number of methodologies available to slow down this pathways, for example removal of water from the protein (see O'Connor, column 2, lines 12-15), adding glycine (see O'Connor, column 1, lines 40-43; column 2, lines 3-5), adding preservatives, non-ionic surfactant and buffer (see O'Connor, column 2, lines 6-8). The skilled artisan would have had reason to try these

methodologies with the reasonable expectation that at least one would be successful. Most of the prior art cited by O'Connor et al has used glycine to stabilize the coagulation of the protein; stabilization of growth hormone using glycine and mannitol; formulation of hGH for lyophilization containing glycine, mannitol, a non-ionic surfactant, and a buffer. Thus, adding different range concentration of components to make a stabilized hGH aqueous formulation is a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

14. In regards to Applicant's argument on neutral salt or mannitol not being part of the instant claims, MPEP states the following: "The transitional phrase 'consisting essentially of' limits the scope of a claim to the specified material or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention. *In re Herz*, 537 F.2d 549, 551-552, 190 USPQ 461, 463 (CCPA 1976)...For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, 'consisting essentially of' will be construed as equivalent to 'comprising.' See e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355...If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of 'consisting essentially of,' applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964). See also *Ex parte Hoffman*, 12 USPQ2d 1061, 1063-1064 (Bd. Pat. App. & Inter. 1989)" See

MPEP 2105. Applicant has not shown in the specification that neutral salt or mannitol would change the characteristic of applicant's invention.

15. In regards to Applicant argument that the Office makes no attempt to establish that O'Connor et al teaches a liquid formulation which has a tonicity of from about 100 to about 500 mosm/kg, O'Connor et al indicates that neutral salts such as sodium chloride or potassium chloride are optionally used in place of sugars or sugar alcohols, and the salt concentration is adjusted to near isotonicity (50-200 mM NaCl) (see column 4, lines 1-6). A person of ordinary skill in the art would have tried to optimize the isotonicity of the liquid formulation. In regards to Applicant argument that there is no prima facie obvious to "select optimal parameters" in a formulation "to achieve a beneficial result", it would have been prima facie obvious to one of ordinary skill in the art to optimize the conditions to produce the optimal formulation, by changing the ranges of the concentrations of components.

16. O'Connor et al teach a kit: six vials of lyophilized growth hormone, water for injection, and six vials of the hGH aqueous formulation transferred to 3 cc vials (see Example II). Furthermore, O'Connor et al teach that addition of preservative is included in the formulation to retard microbial growth and thereby allow "multiple use" packaging of the hGH (see column 3, lines 50-52). Therefore, the reference is prima facie obvious in regards to the instant claims, and the rejection is maintained.

Conclusion

17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claims are allowed.

18. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

20. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

21. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha
Patent Examiner
AU 1654

1/4/12
ANISH GUPTA
PRIMARY EXAMINER